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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/660,301	09/10/2003	Brett P. Giroir	UTSD:1477	5400

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EXAMINER	
CROWDER, CHUN	
ART UNIT	**PAPER NUMBER**
1644	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	04/09/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/660,301	GIROIR ET AL.	
	Examiner	Art Unit	
	Chun Crowder	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01/09/2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-19* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendments, filed 01/09/2007, are acknowledged.

Claims 1-6 have been amended.

Claims 1-19 are pending and currently under consideration.

2. This Office Action will be in response to applicant's arguments, filed 01/09/2007.

The rejections of record can be found in the previous Office Action, mailed 11/29/2006.

3. The three references Garner et al. (Am. J. Heart Circ. Physil. 2003. 285:H2500-H2509), Kurl et al. (Stroke 2001. Sep;32(9):2036-41. Abstract only), and St-Pierre et al. (Am. J. Cardiol. 2003 Mar1;91(5):55-8. Abstract only) cited by applicant have been fully considered and have been listed on PTO-892 herein.

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 1-19 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention for reasons of record.

A) Claims 1-7 are indefinite in the recitation of "cardiovascular risk metric" because the metes and the bounds of the phrase is unclear and ambiguous. The term is neither defined by the claims nor by the instant specification. The specification disclosed the phrase on Summary of the Invention on page 2, however, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonable apprised of the metes and bounds of the claimed "cardiovascular risk metric".

Given the absence of additional rebuttal to the outstanding rejections of record in applicant's amendment, filed 01/09/2007; the rejection is maintained for the reasons of record set forth in the previous Office Action, mailed 11/29/2006.

B) Claims 7-14 and 17 are indefinite in the recitation of "apparently healthy individual" and "the individual is apparently healthy", respectively because the metes and bounds of the phrases are unclear and ambiguous. The phrases are not defined by the claims, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonable apprised of the metes and bounds of the invention. It is not clear what constitutes "apparently healthy individual" and "the individual is apparently healthy".

Applicant's arguments in conjunction with the Giroir declaration and Garner et al. (Am. J. Physiol. Circ Physiol 2003, 285:H2500-H2509) have been fully considered but have not been found persuasive.

Applicant and the Giroir declaration argues that the term "apparently healthy individual" is self-evident to one skilled in the art (e.g. a cardiovascular health professional) and the use of the term in the claims and in the specification on page 3, line 9-13 is consistent with how one skilled in the art would understand this term.

This is not found persuasive for following reasons:

Contrary to applicant's assertions, the metes and bounds of the phrases are unclear and ambiguous. The instant specification on page 3, lines 9-13 discloses that "Apparently healthy individuals have not previously had an acute adverse cardiovascular event such as a myocardial infarction (i.e. individuals who are not at an elevated risk of a second adverse cardiovascular event due to a primary adverse cardiovascular event), and generally do not otherwise exhibit symptoms of disease, particularly acute disease".

One skilled in the art would not be reasonable apprised of the metes and bounds of the "apparently healthy individuals" based on the disclosure of the instant specification; specifically, it is not clear what constitutes the metes and bonds of the symptoms of disease, particularly acute disease.

C) Claims 11-14 are indefinite in the recitation of "characterizing the individual's risk of developing the cardiovascular disorder based upon the combination of the first risk value and the second risk value, wherein the combination of the first risk value and second risk value establishes a third value different from said first and second risk values" because the metes and bounds of the claims are unclear and ambiguous.

Applicant's arguments in conjunction with the Giroir declaration and Garner et al. (Am. J. Physiol. Circ Physiol 2003, 285:H2500-H2509) have been fully considered but have not been found persuasive.

Applicant and the Giroir declaration assert that the phrase is evident to one skilled in the art in view of the specification (e.g. page 3, lines 1-5 and page 6, lines 13-15). The Giroir declaration further asserts that the instant claims are sufficiently clear such that one of ordinary skill in the art to which the invention pertains would understand the metes and bounds of the claims.

This is not found persuasive for following reasons:

Contrary to applicant's assertions, the metes and bounds of the phrase are unclear and ambiguous in view of the instant specification; for example, specification on page 3 lines 1-5 discloses "predictive value of MIF is independent of other predictors and, for example, is additive with other known cardiovascular risk factors, including various prognostic markers of heart disease, such as CRP, serum amyloid A, interleukin-6, homocysteine, total cholesterol, LDL, apolipoprotein B-100, high-density lipoprotein (HDL), and ratio of total cholesterol to HDL, etc. Protocols for using these other markers, including detecting and monitoring methods, are well-known in the art, and this invention generally provides such protocols using MIF as an alternative marker".

Page 6, lines 12-15 of the instant specification discloses "because MIF and LDL cholesterol measurements tend to identify different high-risk groups, screening for both biological markers provides better prognostic information than screening for either alone".

However, the metes and bounds of the claimed "characterizing the individual's risk of developing the cardiovascular disorder based upon the combination of the first risk value and the second risk value, wherein the combination of the first risk value and second risk value establishes a third value different from said first and second risk values" is not provided by the instant specification.

The phrase is not defined by the claims and the specification does not have support for the claimed limitations, and one of ordinary skill in the art would not be reasonable apprised of the metes and bounds of the invention.

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. The specification is objected to as failing to provide proper antecedent basis for the claimed subject matter. See 37 CFR 1.75(d)(1) and MPEP § 608.01(o). Correction of the following is required:

Applicant is required to identify the written support for claims 11-14, particularly the claimed limitation of "characterizing the individual's risk of developing the cardiovascular disorder based upon the combination of the first risk value and the second risk value, wherein the combination of the first risk value and second risk value establishes a third value different from said first and second risk values".

Applicant's arguments have been fully considered but have not been found persuasive.

Applicant asserts that the support for "a third value different from said first and second risk value" is found in original claim 11 and page 3, lines 1-5 and page 6, lines 13-15.

This is not found persuasive because the instant specification fails to provide the proper antecedent basis for the claimed invention.

The meaning of every term used in any of the claims should be apparent from the descriptive portion of the specification with clear disclosure as to its import, see MPEP 608.01(o).

Here, the phrase "a third value different from said first and second risk value", although is in original claim 11, the instant specification does not appear to provide proper antecedent basis for the term; the term is not found in either page.3, line 1-5, nor in page 6, line 13-15 as applicant asserts.

8. Claims 1-19 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention for reasons of record set for the in the previous Office Action, mailed 11/29/2006.

Applicant's arguments, including various citations from the instant specification, in conjunction with the Giroir declaration and the references submitted 01/09/2007 have been fully considered but have not been found persuasive.

Applicant argues that claim 1 comprises a two-step method of determining cardiovascular risk in a person without cardiovascular disease or without a diagnosis thereof (see instant claim 1 for detailed recitation). Applicant asserts that the instant specification enables this two-step method because the methods are:

(i) MIF levels can be determined by a variety of art-recognized methods,

(ii) (a) the step of "assigning to the person a cardiovascular risk metric in accordance with his/her MIF concentration" requires no more than assigning to the person a metric proportional to the MIF concentration,

(ii) (b) prescribing a person a cardiovascular treatment modality in accordance with the person's risk of cardiovascular disease is routine in the art; and the specification on page 4, lines 22-25 discloses such treatment can be anti-inflammatory therapies,

(ii) (c) the recited stress test, CRP assay and LDL assay are well-known and routine to those skilled in the art..

Applicant further argues that claim 7 comprises a three-step method for characterizing a risk of developing a future cardiovascular disorder in an apparently healthy individual and can be practiced by one skilled in the art without undue experimentation; the instant claim 15 is a two-step method for evaluating the likelihood that an individual will benefit from treatment with an agent for reducing the risk of a cardiovascular disorder.

As such, applicant asserts that the claimed method is enabled to one skilled in the art.

This is not found persuasive for following reasons:

Contrary to applicant's assertions that the claimed method is enabled, it is noted that factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed.Cir.1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of the skilled in the art to practice the claimed invention.

Here, the issues are not whether the MIF concentration can be determined, rather the issues are whether MIF concentration can be used as a marker for cardiovascular risk for any person without cardiovascular disease or without a diagnosis thereof, especially it is not clear what constitutes "a control MIF concentration not associated with cardiovascular risk".

The Giroir declaration asserts that the "test" and "control" MIF is both self-evident and inherent in the original claims. However, Applicant and the Giroir declaration both fail to provide sufficient evidence that MIF concentration as claimed can be used in a method of determining cardiovascular risk. The reference Garner et al. (Am. J. Physiol. Circ Physiol 2003, 285:H2500-H2509), submitted in conjunction with the Giroir declaration, teach MIF functions as an important late mediator of endotoxin-induced cardiac dysfunction in mice (see Results on pages H2503-H2505); however, Garner et al. also teach that MIF has an important role in a variety diversified diseases such as rheumatoid arthritis, delayed-type hypersensititvity, inflammatory lung disease, cancer (e.g. see page H2500, in particular). Therefore, Garner et al. support the teachings of (Pan et al. J Vasc Surg 2003. 37:628-635) in that high serum MIF levels have been described in a variety of diseases (see entire document, particularly page 628 and page 632).

For example, patients with rheumatoid arthritis, would be a person without cardiovascular disease or without a diagnosis thereof and would have high MIF concentration but would not necessarily be associated with cardiovascular risk.

Further, the selection of appropriate controls and the interpretation of their results can be controversial, for example, a proper control group needs to be gender and age matched because the MIF levels tended to be higher in men with atherosclerosis, chronic obstructive pulmonary disease, and hypertension, therefore, it's questionable whether it is possible to achieve a control group consisting of 70-year old men without atherosclerosis including subclincal atherosclerosis (see Pan et al. Discussion on pages 632-634). Therefore, it is difficult to decide what constitutes the "a person without cardiovascular disease" and/or an apparently healthy individual to practice the claimed methods.

Regarding applicant's assertion that prescribing a person a cardiovascular treatment modality in accordance with the person's risk of cardiovascular disease is routine in the art; it is not clear what those treatment modality actually is. The specification as-filed on page 4 discloses anti-inflammatory therapies can be used for treating subjects including anti-inflammatory agent. However, the specification provides insufficient guidance to enable one skilled in the art as to how to make and use the claimed method, especially "prescribing for the person a cardiovascular treatment modality".

Furthermore, applicant has not rebutted the teachings of Church et al. (International Journal of Obesity 2005. 29:675-681) and van Dielen et al. (The Journal of Clinical Endocrinology & Metabolism 2004. 89(8):4062-4068) (see page 6 of the Office Action mailed 11/29/2006).

> Church et al. (International Journal of Obesity 2005. 29:675-681), in a study related to obesity, MIF serum concentration and weight loss with 71 severely obese participants, teach that elevation of circulating MIF concentrations are not uniform across individuals; only small percent of the obese participants have elevated circulating MIF concentration (see entire document, particularly Figure 1 on page 676); and it is not clear why some obese individuals have an elevated MIF while others do not; factors such as weight, waist girth, C-reactive protein or any of the cardiovascular disease risk factors are not associated with elevated MIF (see Discussion on pages 679-680).
>
> van Dielen et al. (The Journal of Clinical Endocrinology & Metabolism 2004. 89(8):4062-4068) show that MIF levels in morbidly obese individuals are low, and increase post gastric bypass surgery with decreasing body weight (see entire document, particularly Figure 2A on page 4064 and Discussion on pages 4065-4067). These results are clearly opposite to the disclosure of the instant specification in that the obese individuals have increased serum MIF level (see Examples on page 5-6 of the instant specification).

In conclusion, there is insufficient objective evidence that the skilled artisan would be able to determine cardiovascular risk in a person not predetermined to be subject to cardiovascular disease and/or an apparently healthy individual by accessing MIF concentration given that high serum MIF levels have been described in a variety of diseases and it does not appear a proper control group can be achieved.

In view of the lack of predictability of the art to which the invention pertains, working examples, the state of the art teachings, undue experimentation would be required to practice the claimed invention.

See Office Action mailed 11/29/2006, for detailed analysis.

9. Claims 1-19 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention for reasons of record set forth in the previous Office Actions mailed 07/14/2006 and 11/29/2006.

This is a *Written Description*, New Matter rejection.

The terms "a test MIF concentration" and "a control MIF concentration" in claims 1-19 and the phrase "not associated with cardiovascular risk indicates that the person is subject to elevated cardiovascular risk" as recited in claims 1-6 are not supported by the original disclosure or claim as filed.

Applicant's arguments, including various citations from the instant specification, in conjunction with the Giroir declaration and the references submitted 01/09/2007 have been fully considered but have not been found persuasive.

Applicant argues the terms are self-evident and that the recited predetermined value is a control; applicant further cites page 4, lines 11-16 from the specification as following:

"The predetermined value will depend upon the characteristics of the patient, and/or the relevant patient population. The predetermined value can be a single value, multiple values, a single range or multiple ranges. Thus, in one embodiment, the predetermined value is a plurality of predetermined marker level ranges, and the comparing step comprises determining in which of the predetermined marker level ranges the individual's level falls. In another embodiment, the predetermined value is a historical value from the patient."

However, it is noted that the "predetermined value" is not recited in the instant claims. Further, this *Written Description*, New Matter rejection is against the recited term "a control MIF concentration". It is clear that the definition of predetermined value, on page 4 of the specification where applicant has relied on for support, does not have adequate disclosure for the claimed subject matter.

Applicant further argues that the working example I on page 5 indicated that the determined MIF concentration is a "test" and the compared-to value is a "control".

However, it is noted in Example I of the instant specification, MIF concentration has been determined in several groups and at different time points, it is not clear which of the MIF concentration is "test" and what is the compared-to value.

Therefore, limitations of "a test MIF concentration" and "a control MIF concentration" recited in the present claims, which did not appear in the specification, as filed, introduce new concepts and violate the description requirement of the first paragraph of 35 U.S.C. 112.

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

11. Claims 1 and 2 are rejected under **35 U.S.C. 102(b)** because claims 1 and 2 are anticipated by Yabunaka et al. (Diabetes Care. 2000. 23;2:256-258) for reasons of record set forth in the previous Office Action, mailed 04/17/2006 and 11/29/2006.

Applicant's arguments in conjunction with the Giroir declaration and the references submitted 01/09/2007 have been fully considered but have not been found persuasive.

Applicant argues that Yabunaka et al. teach that the serum MIF did not differ with the clinical stage of the diabetic nephropathy and neuropathy and the possible explanation is that MIF stimulates insulin secretion and MIF secretion is regulated by glucose; as such Yabunaka et al. teach MIF is not a specific disease marker but a nonspecific marker for illness in general.

Applicant further argues that Yabunaka et al. do not teach or suggest the claimed two-step method, nor do they suggest the MIF is a marker for cardiovascular risk.

Therefore, applicant asserts that Yabunaka et al. do not anticipate the instant claims.

This is not found persuasive for following reasons:

Contrary to applicant's assertions, it is noted that the standard for what constitutes proper enablement of a prior art reference for purposes of anticipation under Section 102 differs from the enablement standard under Section 112 because Section 112 provides that the specification must enable one skilled in the art to "use" the invention whereas Section 102 makes no such requirement as to an anticipatory disclosure. See *In re Hafner*, 410 F.2d at 1404.

Here, the finding that the claimed invention is not enabled is supported by substantial evidence based on scientific articles (See Section 7 above).

Further, contrary to applicant's assertion, Yabunaka et al. meet the two step method as claimed because the prior art teaches the first step of first step of determining a test MIF concentration and comparing the test MIF with a control MIF concentration not associated with cardiovascular risk, and the second step of assigning the person a cardiovascular risk metric in accordance with the test MIF concentration, especially given that applicant asserts in the Remarks, filed 01/09/2007, that the step of "assigning to the person a cardiovascular risk metric in accordance with his/her MIF concentration" requires no more than assigning to the person a metric proportional to his/her MIF concentration and is routine in the art (see page 7 of the Remark).

Therefore, the reference teachings anticipate the claimed invention.

12. Applicant's declarations under 37 C.F.R. 1.131 to swear behind reference Garner et al. (Am. J. Heart Circ. Physil. 2003. 285:H2500-H2509) are acknowledged. Given that no rejection has been made using said reference, declarations under 37 C.F.R. 1.131 have not been considered.

13. Conclusion: no claim is allowed.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chun Crowder whose telephone number is (571) 272-8142. The examiner can normally be reached Monday through Friday from 8:30 am to 5:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Chun Crowder, Ph.D.
Patent Examiner
March 20, 2007

PHILLIP GAMBEL, PH.D JD
PRIMARY EXAMINER
TC 1600
3/28/07